Response to Ustekinumab in a Patient with Severe Psoriasis when Adalimumab Dose Escalation Fails

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Abstract: *Objectives*: To report a case of response to ustekinumab in a patient with severe psoriasis when adalimumab dose escalation fail.

Case Description: A 35-year-old Caucasian male was diagnosed as having psoriasis. He was started on methotrexate followed cyclosporine. Despite these treatments, the patient experienced an abrupt deterioration of his psoriasis [PASI 35]. The patient started treatment with adalimumab: initial dose of 80mg followed by 40mg in week 2. At week 3 he continued on adalimumab 40mg/two weeks with significant reduction of psoriasis. After 8 months of adalimumab therapy, he referred that adalimumab was effective only during the first week of treatment. The patient gave his written informed consent for adalimumab dose intensification. He started adalimumab 40mg/week, with an improvement of psoriasis. After 7 months of adalimumab dose intensification, the psoriasis worsened [PASI score =25 and CDLQI score 20]. We discontinued adalimumab and started therapy with ustekinumab, 45mg subcutaneously, was administered at weeks 0, 4 and every 12 weeks. The clinical response was impressive; at week 12 a PASI 90 response was achieved while the CDLQI score fell to the scale of 7. Efficacy was maintained after a 12 months of ustekinumab therapy.

Conclusions: This case report provides valuable insight into the efficacy and tolerability of ustekinumab in a patient with severe psoriasis when adalimumab dose escalation fails. To our knowledge this is the first case published to date that describes the clinical efficacy of ustekinumab when adalimumab intensification dose escalation fails.

Keywords: Ustekinumab, adalimumab, psoriasis, dose escalation.

INTRODUCTION

Psoriasis is an immune-mediated cutaneous disease characterized by the presence of scaly, erythematous plaques [1]. Drug therapy for psoriasis continues to evolve and expand. A small number of systemic therapies are well established in psoriasis management. These have immunosuppressive and/or anti-proliferative effects on the skin and immune system. Conventional non-biologic systemic agents are regarded as first-line therapy for the treatment of moderate-to-severe plaque psoriasis after topical treatments. Biologics offer a unique opportunity to block or inhibit specific key components of psoriasis pathogenesis. The introduction of tumour necrosis factor [TNF] α and interleukin [IL]-12/-23 inhibitors has resulted in remarkable clinical responses in patients with severe psoriasis. Currently, these biological agents [ustekinumab, adalimumab, infliximab and etanercept] are indicated for moderate-to-severe plaque-type psoriasis in adults who fail to respond to, have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA [2].

TNF inhibitors have demonstrated efficacy in psoriasis. Ustekinumab is a fully human monoclonal antibody targeting the common p40 subunit shared by interleukin [IL]-12 and IL-23. Ustekinumab prevents the interaction of IL-12 and IL-23 with their cell surface receptors, and thus blocks T helper [Th]-1 IL-12 and Th-17 IL-23 inflammatory pathways. Ustekinumab has clinical efficacy in adult patients with moderate to severe psoriasis; this is demonstrated by the achievement of high rates of both PASI score and PGA improvement and improvements in quality of life demonstrated by the DLQI [3]. Based on these observations ustekinumab has the potential to provide an alternative therapy for many patients [4].

We present the case of a 35-year-old Caucasian man with severe psoriasis. He was originally treated with methotrexate and cyclosporine with a mild response of his psoriasis Subsequent treatment with adalimumab 40mg/every other week cleared him during 10 months. After adalimumab dose escalation [40mg/week] patient cleared again but only during 7 moths. Switching to ustekinumab showed a marked improvement and completely cleared his psoriatic plaques.

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CASE DESCRIPTION

A 35-year-old Caucasian male [weight 70 kg] was diagnosed as having psoriasis. Past medical history was unremarkable. He was initially started on methotrexate subcutaneous 15mg weekly. After 1 year, Methotrexate was discontinued because of the patient's clinical condition worsened. He was started on cyclosporine 300 mg daily, his clinical condition improved moderately during 8 months. Despite this treatment, the patient experienced an abrupt deterioration of his psoriasis [PASI 35]. The treatment option of phototherapy [either PUVA or UVB] was rejected as impractical, since the patient refused this therapy. We decided to start treatment with adalimumab. A chest X-ray and tuberculin skin test were performed to rule out latent tuberculosis infection. Chest X-ray studies were normal and the tuberculin skin test was negative. The patient started treatment with adalimumab. He received an initial dose of adalimumab 80 mg followed by 40 mg at week 1. At week 3 he continued on adalimumab 40 mg subcutaneously every second week, with significant reduction of psoriasis after 12 weeks. After 8 months of adalimumab therapy a complete resolution of psoriatic lesions could not be achieved. The patient referred that adalimumab was effective only during the first week of treatment. In the literature there are some articles about the clinical efficacy of adalimumab dose escalation [5]. The patient gave his written informed consent for the adalimumab dose intensification. He started adalimumab 40 mg per week, with a significant improvement of psoriasis without any complications. However, after 7 months of adalimumab dose intensification, the psoriasis worsened [PASI score =25 and CDLQI score 20]. At this point, we adalimumab therapy was discontinued. The patient refused to receive infliximab. We considered to change psoriasis target and started treatment with ustekinumab; 45 mg subcutaneously was administered at weeks 0, 4 and every 12 weeks. The clinical response was impressive from the beginning; at week 12 a PASI 90 response was achieved while the CDLQI score fell to the scale of 7. The patient was extremely satisfied with treatment and was almost free of psoriasis, only had to visit the clinic every three months for evaluation and to received ustekinumab injections. The patient no longer experienced symptoms of active psoriasis and was able to forget his disease for most of the time. Efficacy was maintained after a 12 months of continuous therapy (Figure **1**).

DISCUSSION

In the last years, the introduction of biologic drugs has greatly changed the treatment of psoriasis. In fact, tumor necrosis factor-α blockers [TNFb] such as etanercept, adalimumab, and infliximab demonstrated an effective action in controlling symptoms and enhancing quality of life in many patients with psoriasis [6]. In the controlled setting of prospective clinical studies, etanercept, adalimumab, and infliximab had comparable efficacy for psoriasis [7]. Around 45-70% of patients receiving the TNFb therapy achieved at least a PASI 75 response [8]. These data indicate that few patients fail to respond to TNFb treatment, or find that initial efficacy is lost after 6 to 12 months. For these patients switch to another TNFb could be an option [9]. In the case of adalimumab, patients who did not exhibit full response to standard adalimumab dosing regimens are suitable to receive to adalimumab dose escalation. Leonardi *et al.* determined the clinical utility of increasing to weekly adalimumab therapy in patients with psoriasis with inadequate response to every other

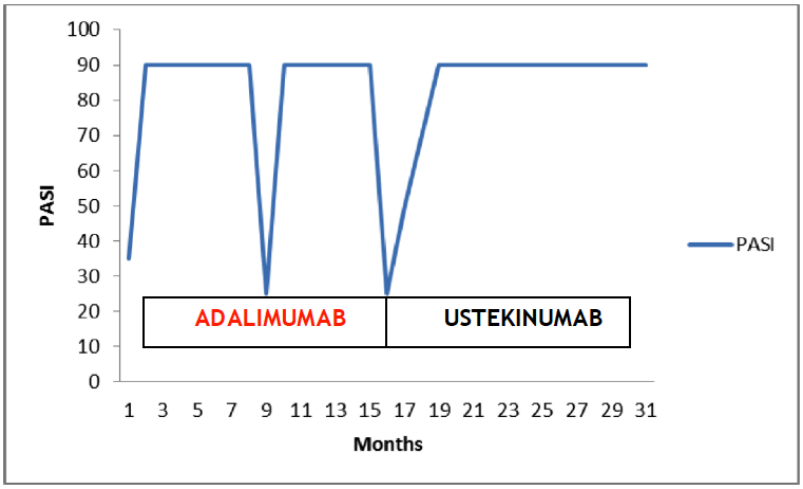

Figure 1: PASI evolution during patient biological drug therapy.

week. 27.8% patients require dose escalation. By 12 weeks after dose escalation, one-quarter achieved substantial clinical improvement. Safety results were similar between patients who dosage-escalated and those who did not [10]. Van den Reek *et al.* showed the effects of dose escalation of adalimumab in patients with insufficient efficacy of adalimumab 40mg/14days. Twenty-five percent of achieved a PASI50 response after 12 weeks and 35% after 24 weeks [11]. In the case we present, adalimumab dose escalation was effective immediately but this initial efficacy is lost after 7 months of treatment. Due to adalimumab dose escalation failed. In these patients, it is possible that TNF blockade is not the best target and other signaling pathways should be considered. For this reason we switched to Ustekinumab, a human monoclonal antibody that binds to the shared p40 subunit of interleukins 12 and 23, it has proved efficacious with around 75% of patients achieving 75% improvement in the PASI75 [12,13].

Based on preliminary observations ustekinumab offers a highly effective therapeutic option in patients resistant to standard therapies. These patients are difficult to treat with TNFb, because in some cases the lack of efficacy of one or more TNFb agent negatively influenced the adherence to another TNFb [4, 14, 15].

Viguier *et al.* showed that non-responders patients to any anti-TNF agents were highly responsive to ustekinumab. Twenty-two patients who were non-responders to all available anti-TNFb were selected and 19 non-responders patients were treated with ustekinumab which led to PASI 75 in all [94%] except one patient after a mean period of time of more than 4 months [16].

Since an economic perspective, adalimumab at labelled dose of 40 mg/14d appeared to be cost-efficacy therapy [17]. Ustekinumab at labelled doses is considered a cost efficacy drug [18]. However adalimumab at off label dose of 40mg/7d; it is possible that high cost affect drug cost effectiveness. We simulated the cost of week treatment with adalimumab as if they had received 40mg/14d, 40mg/7d and ustekinumab during their respective periods. Prices of Humira® 40 mg and Stelara® 45 mg were taken from officially published price bulletins from the Spanish Medication Agency [PVL+IVA]. The cost of treatment with adalimumab at standard dose is 247,3€. However when used in dose intensification scheduled, its weekly cost treatment increased by 50% to 494,6€. Ustekinumab weekly cost treatment is 338,8€. Therefore, since an economic view use of ustekinumab in a patient with severe psoriasis when adalimumab dose escalation fails has a considerable cost impact.

CONCLUSION

This case report provides valuable insight into the efficacy and tolerability of ustekinumab in a patient with severe psoriasis when adalimumab dose escalation fails. To our knowledge this is the first case published to date that describes the clinical efficacy of ustekinumab when adalimumab intensification dose escalation fail.

CONFLICTS OF INTEREST

None disclosed.

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